

## Vagus nerve stimulation

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### Development and licence

The suggestion that vagus nerve stimulation (VNS) could have a role in the treatment of epilepsy was based on its effect on the EEG in animals<sup>1</sup>. Following initial studies, the first human device was implanted in 1988. European Community approval was granted in 1994 and USA (FDA) commercial approval in 1997<sup>2</sup>. More than 45,000 have now been implanted worldwide. VNS currently has a licence in Europe and the UK for the adjunctive treatment of epilepsy refractory to antiepileptic medication. The Epilepsy October 2004 UK NICE guidelines list VNS as indicated 'for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication but who are not suitable for resective surgery' (adults: grade A recommendation; children: grade C recommendation). The US licence is for refractory *partial* epilepsy over the age of 12. The observation that co-existing depression in epilepsy patients seemed to improve with VNS led to further research in this field such that VNS is also now licensed for treatment resistant depression in adults. Other potential therapeutic roles in anxiety, dementia, tremor and obesity are being explored.

### VNS – device and process

Only one system is licensed. The list price cost of the device, excluding implantation, is £7100, and £5500 for the generator when replaced for battery failure. The generator is usually implanted in the left upper chest with the electrodes placed around the left cervical vagus. Contrary to most anatomy textbooks, 80% of vagus fibres are afferent and the parameters used in clinical practice preferentially stimulate these smaller fibres over the efferents. Afferent pain fibres may be activated, especially at higher levels of clinical stimulation, producing discomfort in the throat. In some experimental animal models stimulating the right vagus nerve produces cardiac dysrhythmias so it is only licensed for implantation on the left in humans. Where, for a variety of reasons, it has been implanted on the right, there have been no sequelae however<sup>3</sup>.

An electrical test of the device is performed intra-operatively but the device is usually activated some time post-operatively, often at the first outpatient follow-up. Continuous electrical stimulation of the vagus nerve in animal models has been shown to produce fibrosis and ultimately failure of the nerve, so stimulation is provided in an intermittent manner. Typically it is initially set to provide 30 seconds' stimulation every five minutes. The device is programmed externally (output current, signal frequency, pulse width, signal on- and off-times) and adjustments are made on the basis of tolerability of side effects and clinical efficacy. In addition to the continuing cycling on and off, it is possible manually to activate the device by passing a magnet over the generator box. Patients or carers can use this when a seizure starts, and in some the magnet seems to shorten or limit the extent of the attack. Commonly the current delivered following magnet-induced activation is set slightly higher than the regular level. The magnet also provides a means for the patient to

deactivate the device. If the magnet is placed over the generator box and it remains there for more than a few seconds it becomes switched off. When the magnet is subsequently removed, it reactivates at the previous settings. Regular follow-up is needed with gradual current adjustment to achieve maximum benefit in a similar way to adjustments of antiepileptic drug (AED) dose. Battery life, which depends on output and magnet use, is now likely to exceed six years even at higher output levels, after which the pulse generator will need to be replaced. The device should be checked regularly and an early replacement indicator (ERI) or 'near end of service' (NEOS) alert will warn the clinician of impending battery exhaustion.

### **Mechanism of action**

This is not established<sup>4,5</sup>. Afferent pulses reach the nucleus tractus solitarius (NTS), synapsing bilaterally. The NTS projects to the thalamus, hypothalamus, locus coeruleus, reticular activating system, midline raphe, limbic system and secondarily to the cortex. Animal studies have looked into various possible mechanisms and effects. VNS is thought to have an effect on EEG synchronisation. In a maximal electroshock rat epilepsy model, VNS therapy was no longer effective as an anticonvulsant when noradrenergic pathways were depleted by lesioning of the locus coeruleus. A cat amygdalar kindling seizure model suggested a partial anti-epileptogenic effect of VNS. Positron emission tomography (PET) scanning showed increased blood flow in the thalamus, hypothalamus, and the insular cortex with decreased blood flow in the amygdala, hippocampus, and posterior cingulate. VNS induced forebrain Fos, a nuclear protein expressed under conditions of high neuronal activity. Studies in humans treated with VNS have included electroencephalography, evoked potential recordings, imaging for changes in blood flow and CSF studies.

Theories regarding mechanism of action of VNS include direct activation, neurotransmitter and neuropeptide modulation influencing ictal discharge, pre-ictal changes and arousal<sup>4,5</sup>.

### **Precautions and adverse effects**

Despite little vagal visceromotor activity during therapeutic VNS in humans, caution is advised in patients with heart disease and severe asthma. One study concluded that 'long-term vagus stimulation in patients without concomitant lung disease does not induce any significant changes in FEV1. However, in patients with obstructive lung disease, intense vagus stimulation can cause a deterioration of lung function'<sup>6</sup>. Transient bradycardia or sinus arrest may occur intra-operatively during the lead test in 0.1% of cases but is not a contraindication to switching on the device after an interval. Infection of the lead or generator site may occur in up to 3% requiring removal of the device in about 1%. Lead breakage may occur. Horner's syndrome, unilateral facial weakness and vocal cord paresis have been reported. Stimulation and, to a lesser extent, implantation may be associated with hoarseness, cough, dyspnoea, paraesthesia and pain. Pre-existing dysphagia may be exacerbated, as can obstructive sleep apnoea.

Common side effects of ataxia, dizziness, fatigue, nausea and somnolence related to AEDs were absent from the Cochrane review from the list of statistically significant side effects.

### **Practical considerations**

Strong electric or magnetic fields may damage the generator and should be avoided. A detailed account regarding risks associated with defibrillation, lithotripsy, therapeutic ultrasound and therapeutic and surgical diathermy can be found on the website [www.cyberonics.com](http://www.cyberonics.com). The system is not affected by home microwave ovens or mobile

phones. Airport security systems and shop theft detectors may be activated by VNS. There are restrictions with MRI to avoid tissue damage through heating the lead, though most head MRIs can be performed using transmit-and-receive head coils. MRI should not be performed using a body coil in transmit mode which, in practice, means body or spinal MRI is prohibited. There is no data on transmit-and-receive local coils such as used for imaging extremities.

### **Effect in epilepsy**

VNS appears to have an abortive and a prophylactic effect, both acutely and chronically in epilepsy. It is effective in various animal seizure models. Although the double-blind studies were in partial epilepsy, it appears to be broad spectrum. It has been implanted in a variety of syndromes, including idiopathic generalised epilepsy and Lennox-Gastaut syndrome<sup>7</sup>.

There have been only two double-blind randomised controlled trials in partial epilepsy<sup>8,9</sup>. It has been argued that mean reductions of seizure frequencies of 24.5% and 28% observed at three months in these trials indicate rather modest benefits. However these values are not very different to figures for add-on AEDs in similar refractory patients and, by contrast with AEDs whose benefits tend to reduce with time, open studies consistently show an increasing effect of VNS with time. For example, at one year a median seizure reduction of 45% has been shown, with 20% of patients achieving a greater than 75% reduction<sup>2,10,11</sup>. However periods of seizure freedom greater than one year are only experienced by about 5% of patients in the open studies and may be subject to considerable publication bias<sup>7</sup>. Additionally it appears that VNS may have additional beneficial effects, including reduction in seizure severity, reduction in epilepsy-associated co-morbidity (mood, cognition and behaviour) and a longer-term cumulative prophylactic effect<sup>9</sup>.

Interestingly, a mortality study by Annegers<sup>12</sup> showed that the excess mortality associated with refractory epilepsy was lower with longer-term follow-up (standardised mortality ratio, or SMR, of 3.6 with extended follow-up compared to the previous finding of an SMR of 5.3). Moreover, when VNS experience was stratified by duration of use, the rate of sudden unexpected death in epilepsy (SUDEP) was 5.5 per 1000 over the first two years and 1.7 per 1000 thereafter, perhaps reflecting the gradual increase in efficacy over time.

In a cost analysis study<sup>13</sup>, unplanned direct hospital costs before and after VNS implantation showed an annual reduction of some \$3000 US per study patient, irrespective of whether the patient was classified as a responder (in this study defined as experiencing 25% or greater reduction in seizure frequency). Another study reported a significant decrease in epilepsy-related direct medical costs in VNS treated patients<sup>14</sup>.

A Cochrane review (2001) addressed the efficacy of high-level versus low-level stimulation, the latter as active control<sup>15</sup>. The review only included the same two early short-term randomised and double-blind trials<sup>8,9</sup>. The review concluded that 'that results of the overall efficacy analysis show that VNS stimulation using the high paradigm was significantly better than the low stimulation'. The overall odds ratio (OR) for 50% responders was 1.93 (1.1, 3.3). Any beneficial effect of low stimulation would tend to reduce the high stimulation OR compared to placebo. Although direct comparisons may well not be valid, of interest are ORs reported in meta-analysis of studies of some add-on AEDs. For example ORs reported for 50% responders relative to placebo were, in order of increasing magnitude: 1.59 (0.91, 2.97) for remacemide, 2.29 (1.53, 3.43) for gabapentin, 2.32 (1.47, 3.68) for lamotrigine, 2.46 (1.61, 3.79) for zonisamide, 2.51 (1.88, 3.33) for oxcarbazepine, 3.78 (2.62, 5.44) for levetiracetam and 4.22 (2.80, 6.35) for topiramate<sup>16,17</sup>. Thus VNS in early studies appears to have a short-term effect in refractory patients

approaching that of some of the AEDs. It is less effective, however, in the short or long term, than resective surgery in well-selected cases, including temporal lobectomy for mesial temporal sclerosis. Clearly controlled data for longer-term outcome is required to confirm the open studies discussed above. This is being addressed through two current studies: PULSE in adults and E06 in children, which should provide more robust figures by about 2009.

## Summary

VNS offers a different approach, advantages and disadvantages to standard AEDs and its profile may preferentially suit many patients. It is now established as a safe procedure with clear, clinically useful and sustained benefits, particularly in the medium to long term. It is, however, no panacea as seizure freedom rates so far are low and concomitant AEDs are needed. Since compliance is not an issue and given the absence of CNS-type side effects, its use is likely to increase and be extended; caution should still be exercised in older populations with potential co-existing cardiopulmonary disease where experience is still limited. Its use earlier on in the course of the epilepsy shows promise and requires further assessment. Guidance in relation to generator replacement in responders still needs to be established<sup>18</sup>. Studies will compare the efficacy of adjunctive VNS vs adjunctive AED treatment. It remains to be seen if VNS has a useful *antiepileptic* effect and where its future will be in relation to other emerging functional procedures<sup>19</sup>. The successful introduction of VNS has undoubtedly opened the path for different approaches to the treatment of epilepsy from those of ‘more pills or cutting out bits of brain’.

## Addendum

Since the above chapter was written in 2007 there have been a number of publications on the use of VNS in epilepsy and more widespread acceptance of its role and efficacy, in relation not only to reduction of seizure frequency but also to reduction in seizure severity and in improved alertness. For example, in a review of 26 consecutive children who had VNS implantation for refractory epilepsy followed up for a minimum of 18 months from Melbourne, Australia, 54% responded with  $\geq 50\%$  seizure frequency reduction, with a higher response rate in those with Lennox-Gastaut syndrome and tonic seizures<sup>20</sup>. Other benefits included reduction in status episodes and improvement in seizure severity, duration, and recovery time, with increased alertness reported in all responders and a few non-responders. The authors concluded that there were benefits over and above the benefit from seizure frequency reduction, namely decreased seizure severity, recovery time, and hospitalisation due to status and abolition of daytime drop attacks. A multicentre study (E06) of earlier use in children is ongoing.

There is however some concern regarding limitations of new generation MRI in those with VNS implantation, including those where the device has been removed but the wire remains. The potential risks of performing MRI on patients with an implanted VNS include heating effects, especially of the stimulation electrodes, inadvertent resetting of the device or magnet mode activation, image distortion and artefacts, magnetic field interactions and device malfunction or damage. If performing an MRI scan, VNS output should be set to zero beforehand and reset afterwards, meaning that an appropriately trained person must be available. VNS is approved in MRI scanning using only transmit-and-receive type head coils at both 1.5 and 3T field strength. Some modern head coils are of the phased-array type which should not be used however. In practice, good diagnostic quality brain scanning can be achieved if appropriate precautions are in place, however body or extremity imaging (receive only coils) and experimental brain protocols are not possible even probably if the

generator has been explanted and only the wire remains. It is advisable to consult the device manufacturer if there is any doubt.

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